



Cutaneous or Mucosal Delivery of Anthrax rPA Provides Protection against Inhalational Anthrax

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Overview of Presentation

- I. Introduce BD Advanced Vaccine Delivery Platforms
 - Cutaneous Delivery
 - Intranasal Delivery

- II. Progress of BD / USAMRIID collaboration
 - Anthrax rPA Vaccine Studies

- III. Summary and Next Steps

Attributes of BD Advanced Drug Delivery Platforms

- **Safety:** *low possibility of secondary infection*
- **Efficacy:** *enablement of new vaccines, improvement of existing vaccines, and enablement of new clinical practices*
- **Ease of use:** *minimal training necessary*
- **Dispersibility:** *fully loaded unit dose disposables*
- **Favorable system economics:** *overall cost of immunizations lowered vs standard practice*

These attributes represent major unmet needs for biodefense vaccination

BD Advanced Vaccine Delivery

**Intradermal
Delivery**

Microneedles

- Pain Minimized
- Enhanced Drug delivery
- Immune Response



**Epidermal
Delivery**

Microarrays

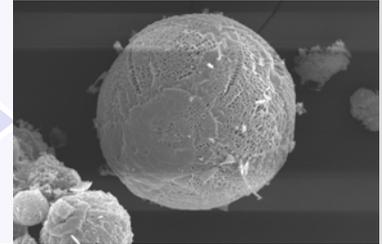
- Pain Free
- “Swipe and Go”
- Enhanced Immune Response



**Formulation
Technology**

ALP Powder

- Instant Reconstitution
- Enhanced Stability
- Suitable for ID, IN, ED



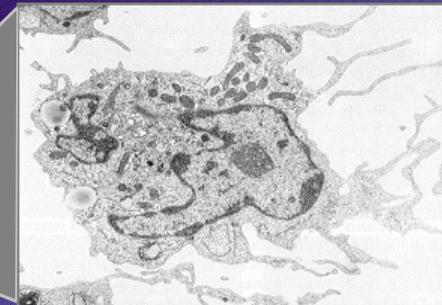
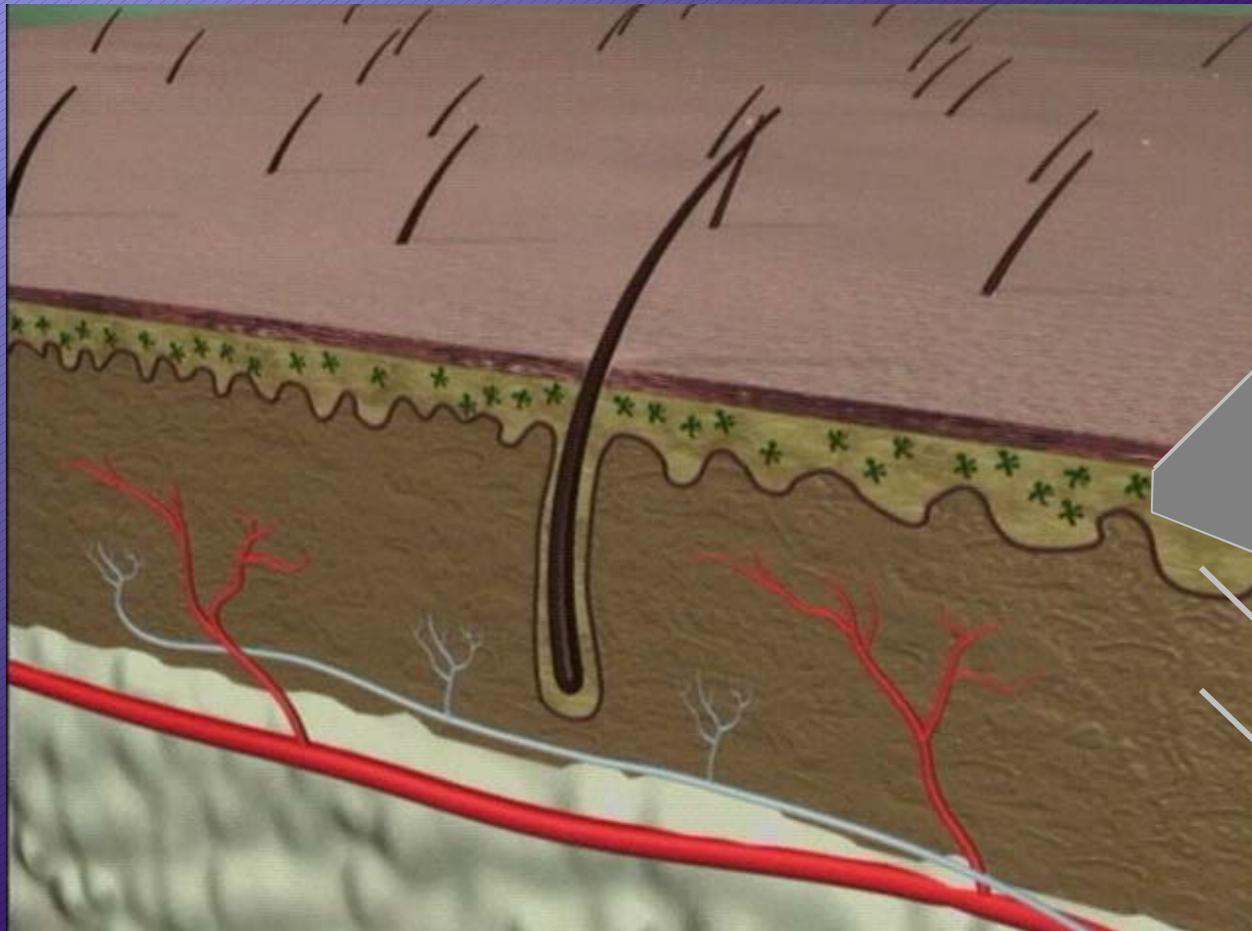
**Intranasal
Delivery**

**Propelled
Mist or Powder
from Proprietary
Nebulizer**

- Pain Free
- Effective Immune Response



Epidermal Delivery via Onvax Microabrasion Technology



Langerhan's cell

Epidermis

Dermis



BD OnVax

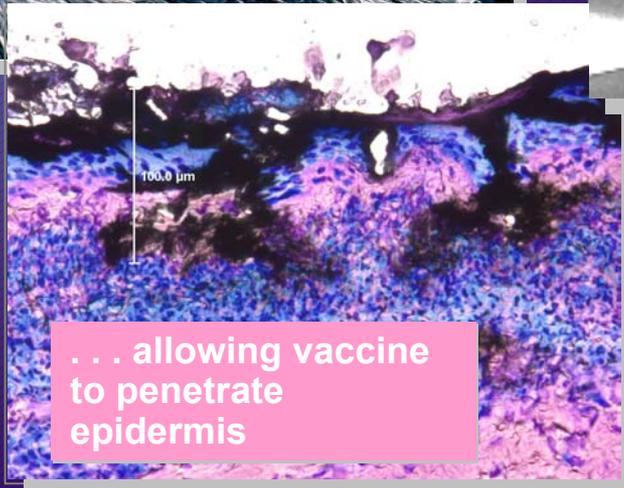
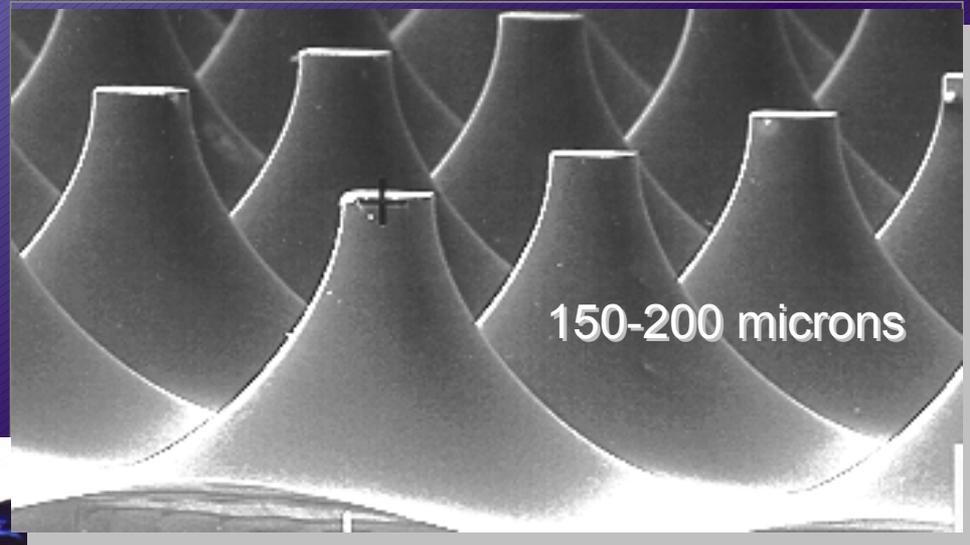
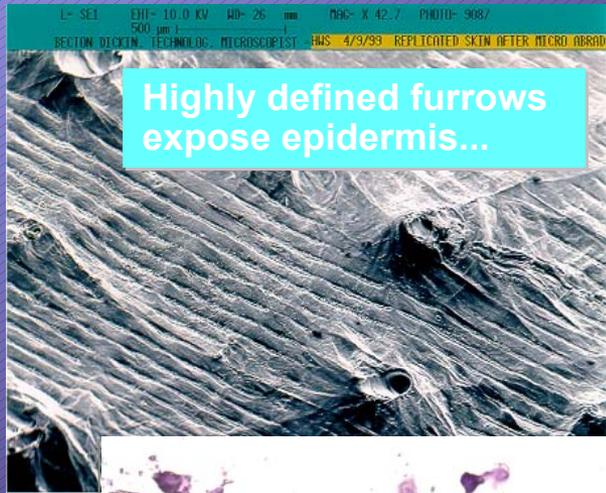
US Patent 6595947
US 09/405488 allowed

OnVax Platform Provides “Wipe & Go” Vaccine Delivery



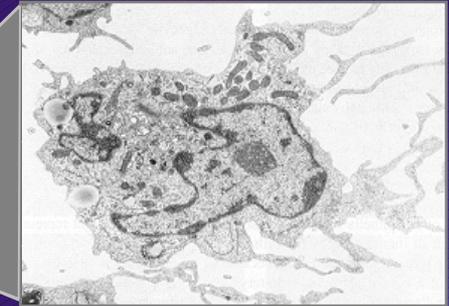
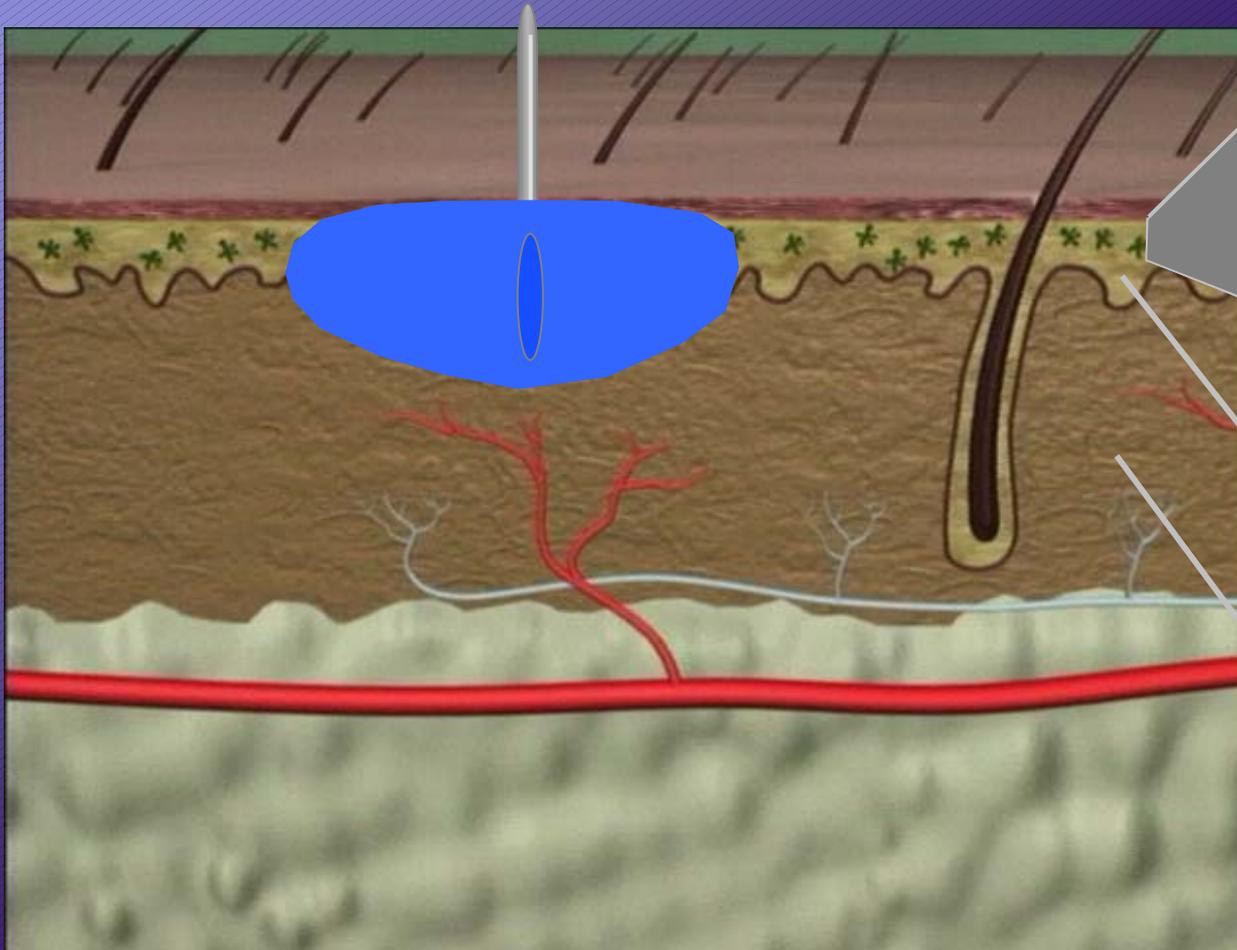
- direct access to antigen presenting cells in dermis
- “wipe & go” vaccination
- easy self administration
- easy clinical administration
- painless

OnVax is a Minimally-invasive Platform for Epidermal Vaccine Delivery



- OnVax devices gently expose Langerhans cells to vaccines without painful injections

MicroMedica employs microneedles for shallow intradermal delivery



Langerhan's cell

Epidermis

Dermis

100µm*

Becton Dickinson Technologies Microscopist=HWS Two mm Three Needle Array //Swine Skin



**MicroMedica delivers
vaccine to the shallow skin**

BD Intradermal Delivery Products Under Development

ID Syringe



Automatic Injector



Microinfusor



MicroMedica Platforms are Designed for Reliable Shallow ID Delivery

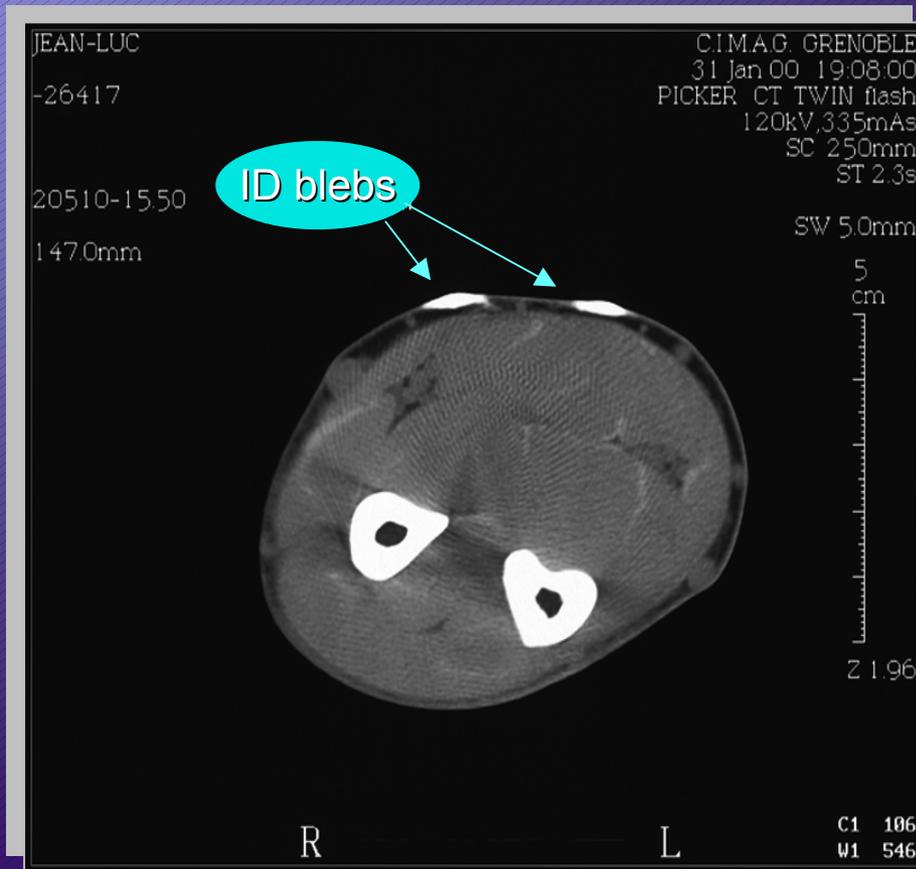


MicroMedica platforms provide:

- vaccine delivery into epidermis/upper dermis
- direct access to APCs and lymph circulation
- easy self administration
- easy clinical administration

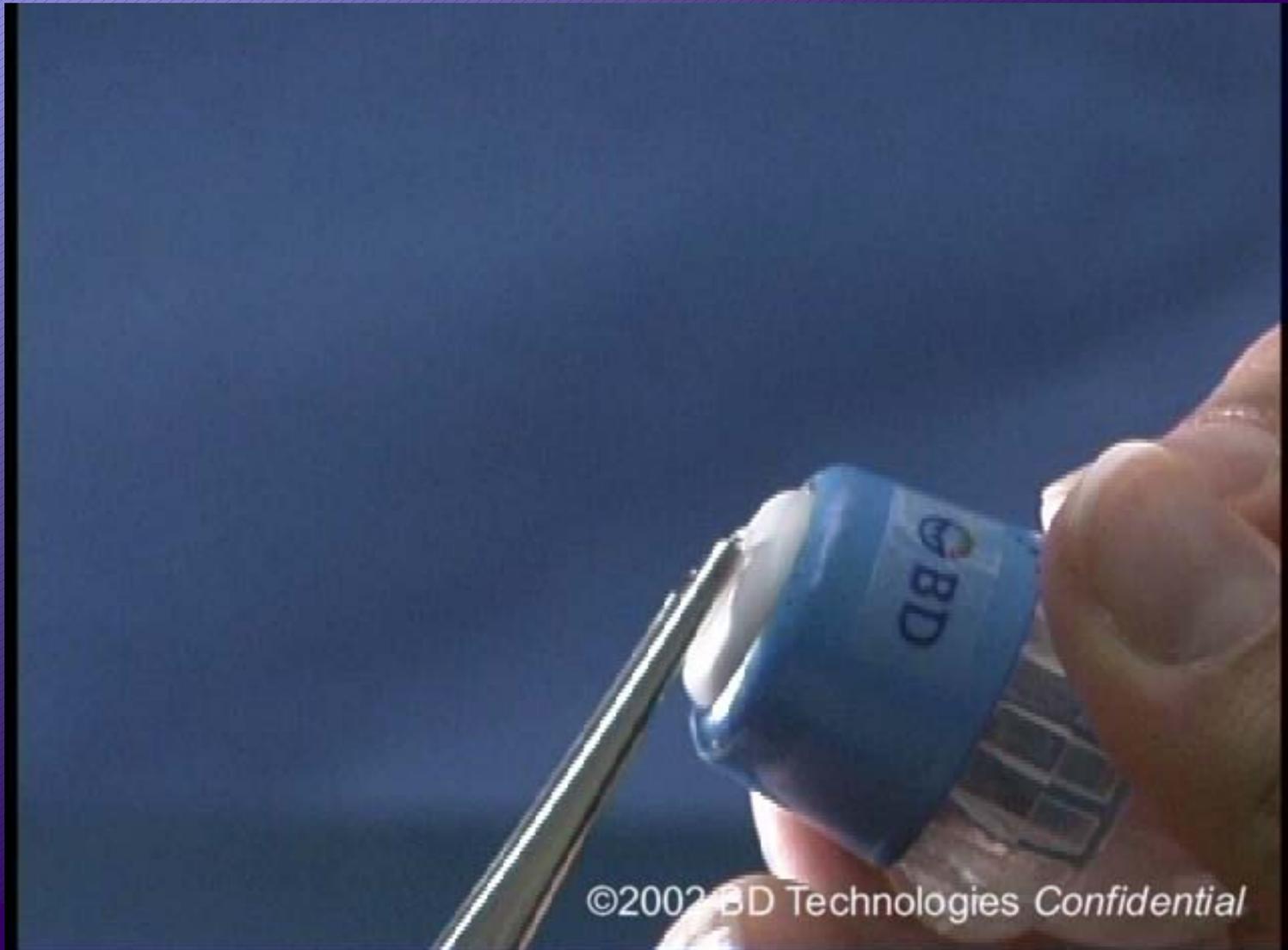
Yorkshire Swine Model

CT Scan Visualization of ID Delivery in Human Forearm



- Contrast agent located in dermis
- No SC contamination
- Controlled delivery

BD Auto-Injector is Designed for Self-Administration



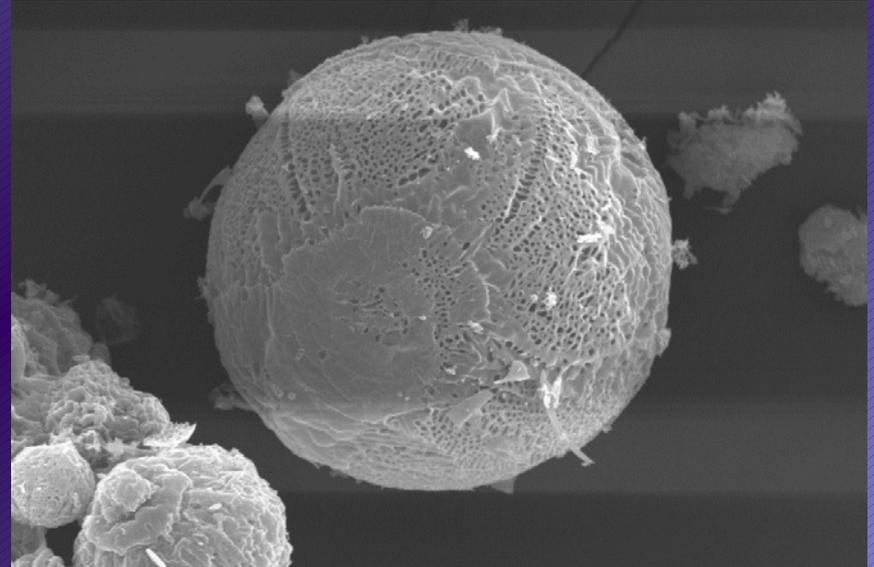
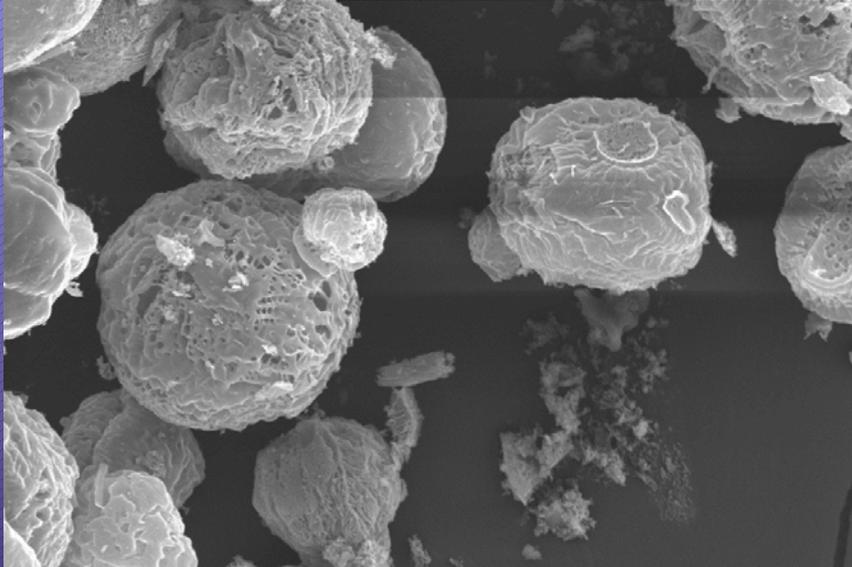
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BD Advanced Drug Delivery



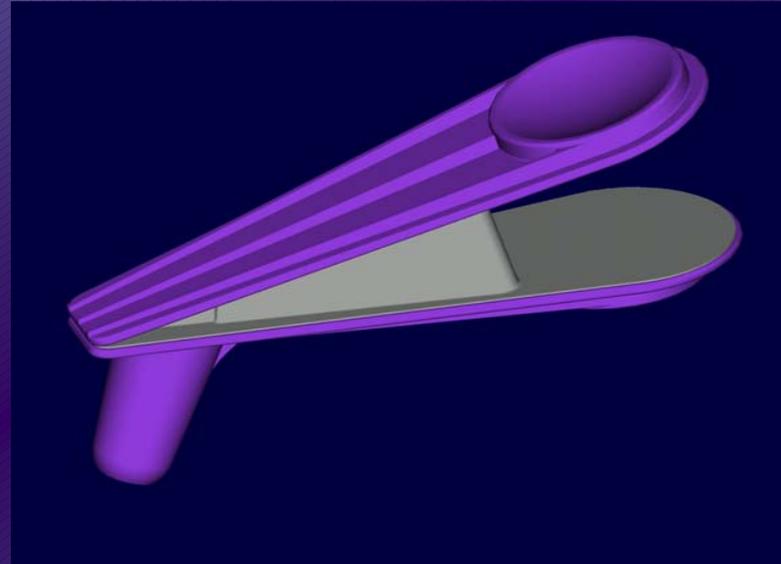
Helping all people
live healthy lives

Aerodynamically Light Powder (ALP) rPA Formulations Developed



ALP powders suited for rapid reconstitution
injection as well as direct intranasal delivery

SoloVent™ Nasal Delivery Platform



- Low cost, robust, ergonomic design
- Prototype testing underway

SoloVent Provides Non-Invasive Needle-Less Vaccine Delivery



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No other commercial offering combines Solovent's ease of use with high efficiency delivery of therapeutics and vaccines.

CRADA UPDATE

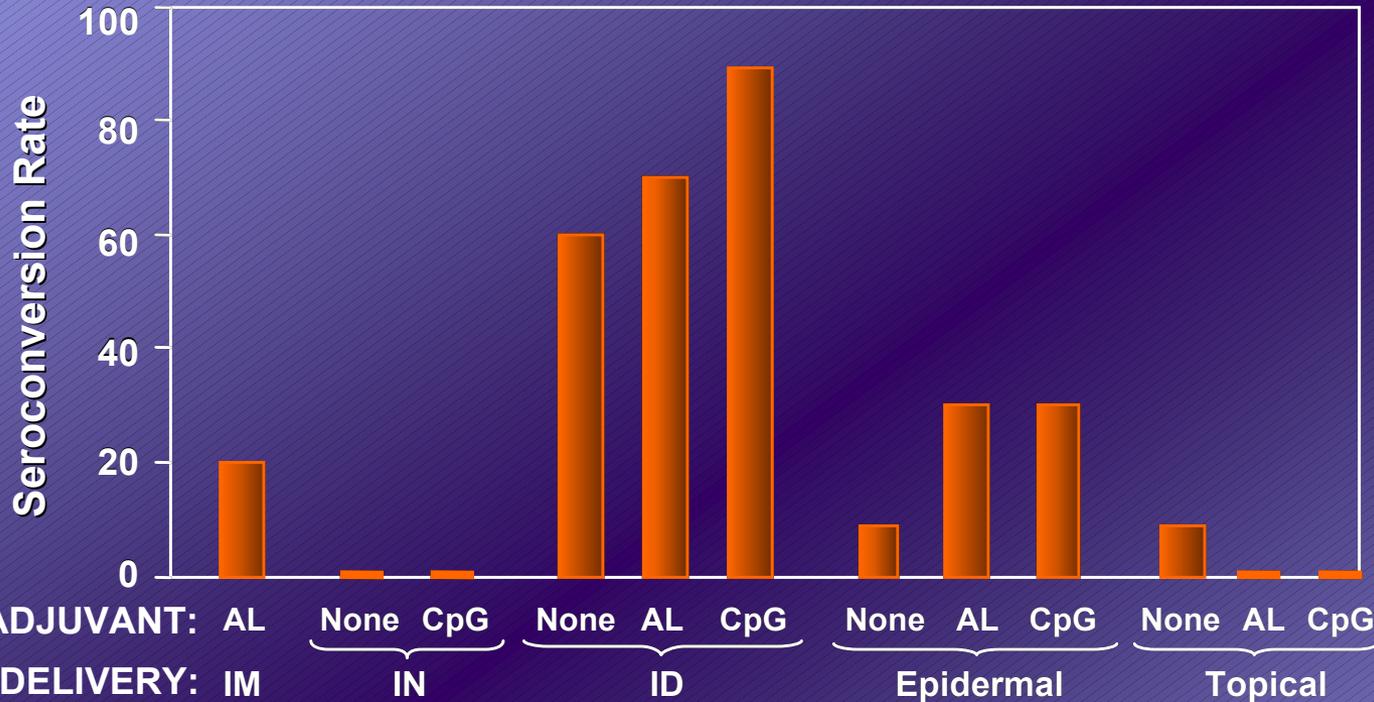
- Progress of BD / USAMRIID collaboration
- Anthrax (rPA) Vaccine Studies
 - Immunogenicity in mice
 - Lethal Challenge in rabbits

Anthrax rPA: Mouse Immunogenicity Study Design

- Compare efficacy of various delivery routes
 - MicroMedica-based ID delivery
 - OnVax-based topical delivery
 - Topical (no device)
 - IM injection
 - IN instillation (liquid formulation)
- Adjuvant comparison (Alhydrogel, CpG or none)
- BALB/c female mice (n=10/group)
- Dosed with 10 μ g rPA on d0, d21 and 42
- Sera collected at d0, d21, d42 and d56
 - PA-specific antibody titers by ELISA
 - PA / LT-neutralizing antibody titers in monocyte cell cultures

Rapid sero-conversion following ID delivery of anthrax rPA in mice (ELISA Titers)

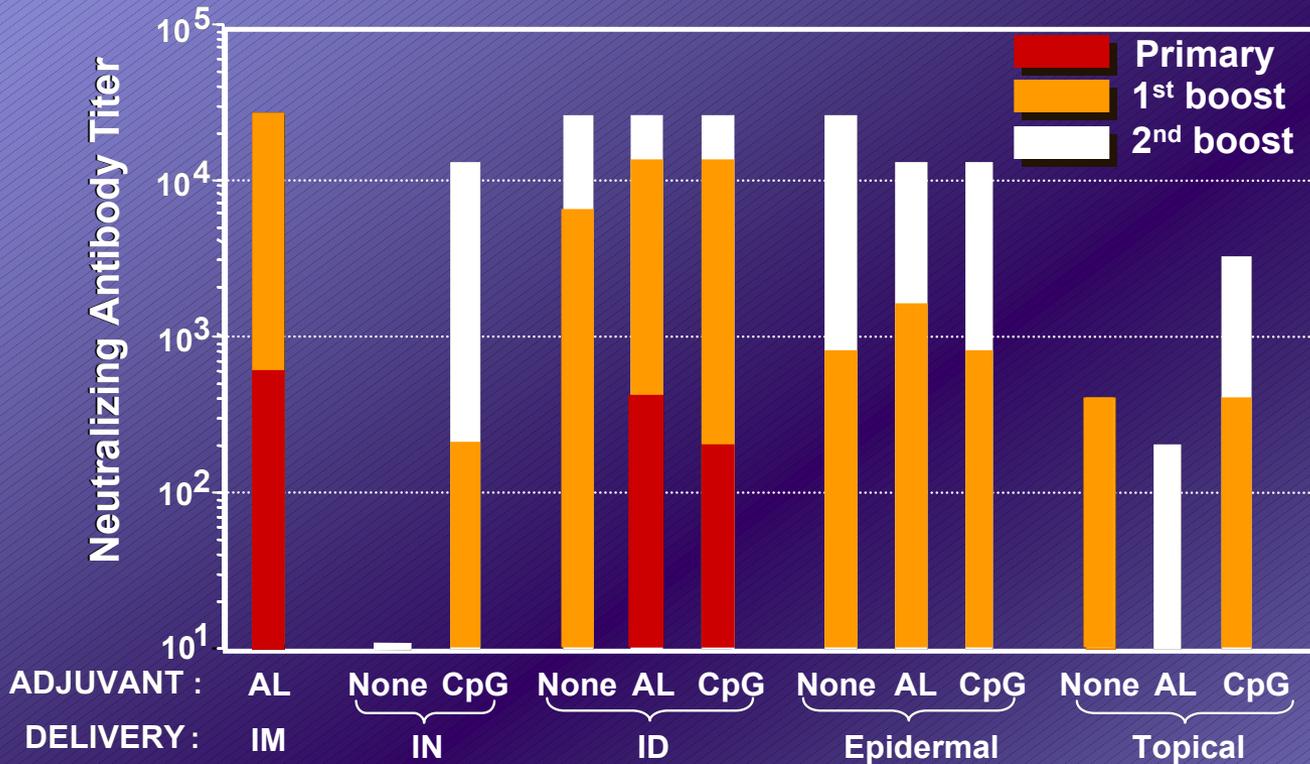
% Seroconversion after 1 dose of vaccine



ID delivery provides:

- Up to 90% seroconversion after a single dose
- Significant seroconversion (60%) even without adjuvant

Induction of Anthrax Toxin Neutralizing Antibodies in Mice

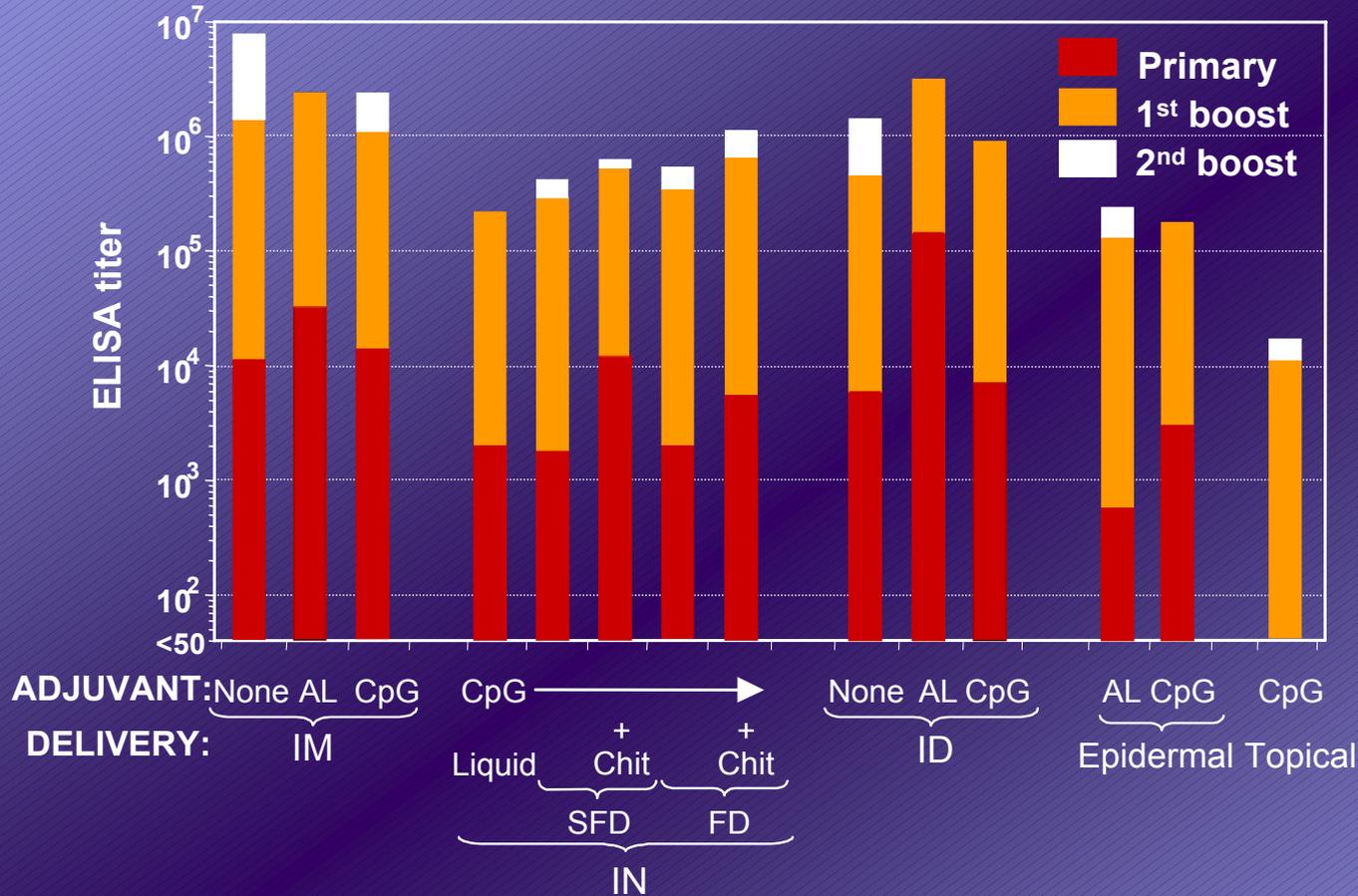


- Only ID and IM induce TNA after single dose
- IN and epidermal delivery required 3rd dose to reach comparable TNA as via IM and ID

Anthrax rPA: Rabbit Challenge Study Design

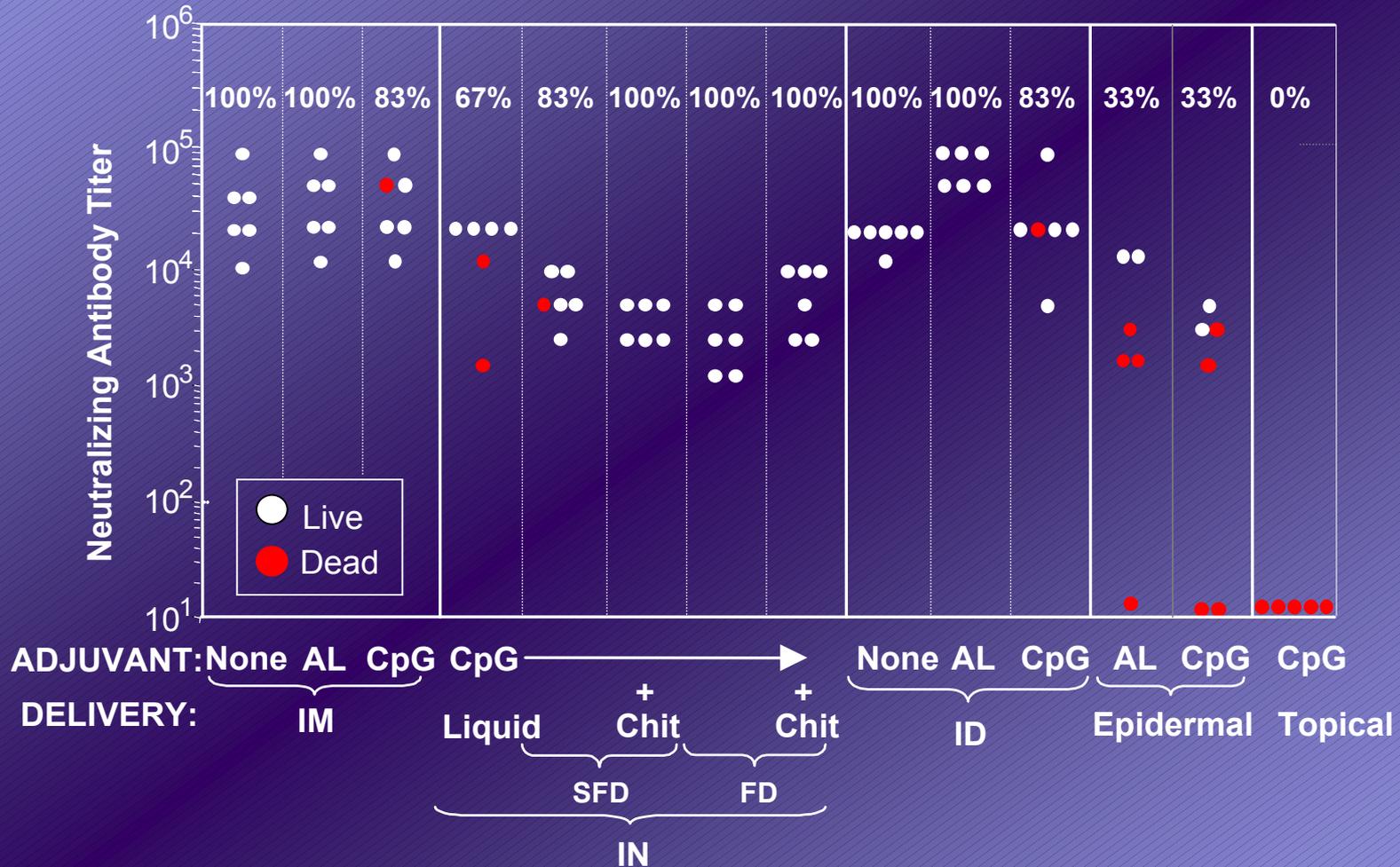
- Compare protective efficacy of various delivery routes
 - MicroMedica-based ID delivery
 - OnVax-based topical delivery
 - Topical (no device)
 - IM injection
 - IN instillation (liquid formulation)
 - IN delivery (ALP powder formulation and SoloVent device)
- Adjuvant comparison (Alhydrogel, CpG or none)
- NZW female rabbits (n=6/group)
- Dosed with 50 μ g rPA on d0, d21 and 42
- Sera collected at d0, d21, d35 and d56
 - PA-specific antibody titers by ELISA
 - PA / LT-neutralizing antibody titers in monocyte cell cultures
- Aerosol challenge with ~100 LD50 anthrax spores

Antibody Response (ELISA) in Rabbits



- IM and ID-induced titers strongest
- No major adjuvant effect

ID and IN powder delivery provide complete protection against lethal aerosol challenge



Summary of Anthrax Studies

- *First demonstration of complete protection against inhalational anthrax via cutaneous or mucosal vaccination*
- Powder vaccine provides better protection than liquid formulation administered IN
- Onvax-based epidermal delivery provides partial protection – potential to improve with modifications in device design and/or vaccine formulation
- Additional studies required to evaluate potential dose sparing advantages from ID delivery and powder formulations

Next Steps

- Human clinical trial to evaluate ID delivery of rPA anthrax vaccine
 - Johns Hopkins University School of Public Health
- Dose reduction studies for anthrax rPA vaccine in rabbits
- Optimize storage stability of powder and liquid rPA vaccine formulations
- Accelerate development of ID auto-injection platform
- Feasibility studies with additional biodefense vaccine candidates (Staphylococcal toxic shock, botulism, others...)

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